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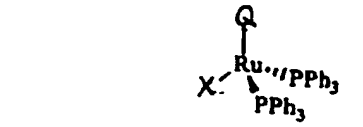
[Continued on next page]

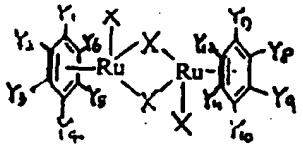
(54) Title: PREPARING METHOD OF CHIRAL ESTER



(1)

(a)

(b)



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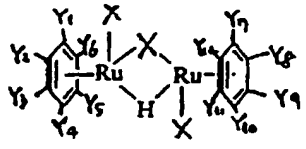

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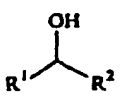

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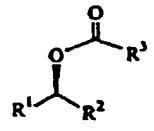

(100)

(57) Abstract: The present invention is to provide a process for preparing a chiral ester expressed in formula (100) by reacting; a racemic alochol of formula (4); a ruthenium complex selected from the group consisting of compounds 1,2 and 3 expressed in formulas (1),(2), and (3) to activate racemization of said racemic alchol; a lipase to acylate one enantiomer selectively from said racemic alcohol; and an acyl donor compound to supply acyl group to said lipase, formula (1) wherein Q is (a) or (b); and X is Br, Cl or I; formula (2) wherein Y_1,Y_2,Y_3,Y_4,Y_5,Y_6,Y_7,Y_8,Y_9,Y_{10},Y_{11} and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; formula (3) wherein Y_1,Y_2,Y_3,Y_4,Y_5,Y_6,Y_7,Y_8,Y_9,Y_{10},Y_{11}, and Y_{12}, are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and formulae wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R' and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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PREPARING METHOD OF CHIRAL ESTER

BACKGROUND OF THE INVENTION

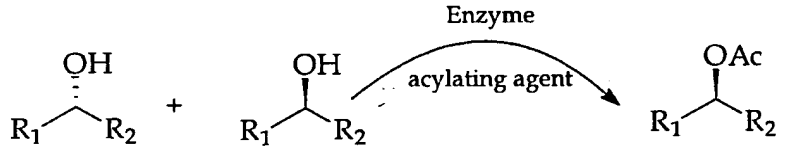
Field of the Invention

The present invention relates to a method for preparing a chiral ester and more particularly, the method for preparing an optically pure chiral ester from a racemic alcohol at a high yield.

Recently, studies for using a metal or an enzyme as a catalyst have been increased in asymmetric syntheses. It has been widely known to use an enzyme as a catalyst for kinetic resolution of a racemic mixture in organic syntheses. A variety of effective methods for hydrolysis of an ester and acylation of an alcohol in the presence of lipase as a catalyst has been reported.

Kinetic resolution is the fact that the two enantiomers react at different rates with a chiral addend. An effective kinetic resolution is the enantioselective conversion from a racemic mixture to an optically pure product as shown in scheme 1, leaving the other enantiomer in a reaction medium.

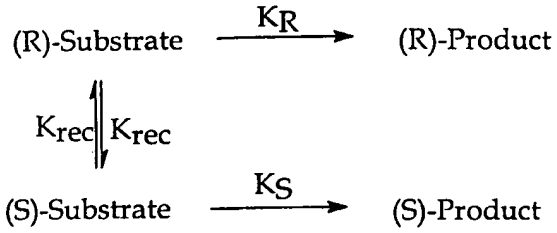
Scheme 1



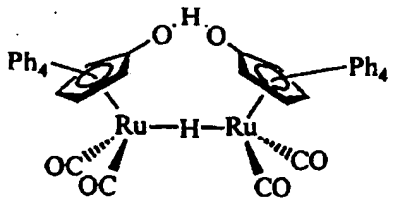
It is well known to prepare a chiral ester from a racemic alcohol by kinetic resolution using esterase. It is possible to obtain an optically pure ester but a maximum yield of this reaction is limited to 50% as shown in scheme 1. Therefore, dynamic kinetic resolution performing kinetic resolution and racemization of an alcohol simultaneously is introduced to resolve such

problems (scheme 2).

Scheme 2



The well-known example of a dynamic kinetic resolution is the reaction by using ruthenium complex expressed in the following structure and lipase (Novozym 435) [B. A. Persson, A. L. E. Larsson, M. L. Ray, and J. E. Backvall, *J. Am. Chem. Soc.* 1999, **121**, 1645].



Because racemization of a starting material is performed simultaneously with kinetic resolution, the effectiveness of the starting material is very high and thus, yield of obtaining (R) or (S) enantiomer is theoretically 100%. However, even if the optical purity of a chiral ester obtained by dynamic kinetic resolution is 99 e. e.%, 12 to 40% of ketone as a by-product is produced.

SUMMERY OF THE INVENTION

Therefore, an object of the present invention is to provide a process for preparing an optically pure chiral ester from a racemic alcohol by dynamic kinetic resolution with minimum production of a ketone.

Detailed Description of the Invention

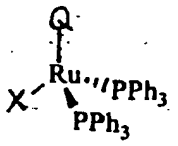
A process for preparing a chiral ester of the present invention is characterized by reacting:

a racemic alcohol;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate racemization of said racemic alcohol;

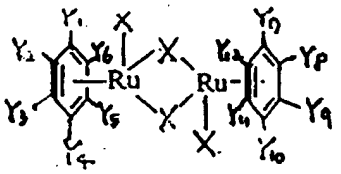
a lipase to acylate selectively one of enantiomers of said racemic alcohol; and

an acyl donor group to supply acyl group to said lipase,



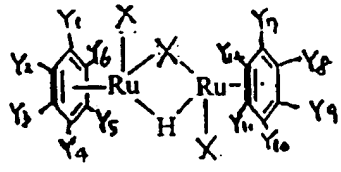
(1)

wherein Q is  or  ; and X is Br, Cl or I;



(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;

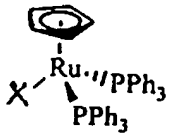


(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a

hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I.

Said ruthenium complex is selected from the group consisting of the compounds 5 to 12 expressed in the following formulas 5 to 12,



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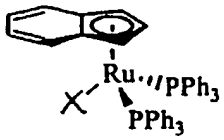

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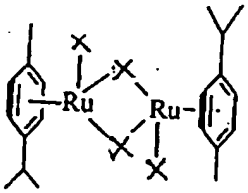

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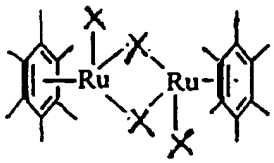

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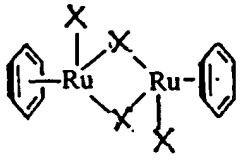

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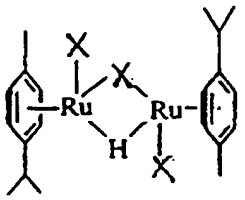

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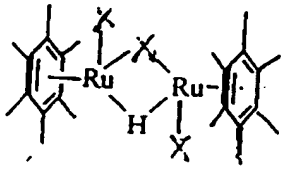

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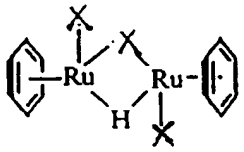


(12)

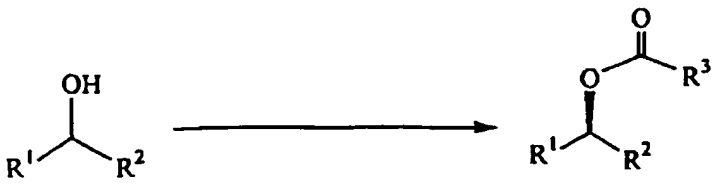
wherein X is Cl, Br or I, the most preferably Cl.

Preferred content of ruthenium complex is 0.1 to 5 mol%, relative to a racemic alcohol. If the content is more than 5 mol%, cost becomes expensive. On the other hand, if it is less than 0.1 mol%, the rate of the reaction becomes too slow.

A method for preparing a chiral ester from a racemic alcohol by dynamic kinetic resolution is described in detail as set forth hereunder.

A mixture of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is reacted in a solvent in the presence of a base shown in Scheme 3,

Scheme 3



(4) (100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

A reaction condition varies with a structure of ruthenium complex. When the ruthenium complex of formula 6 is used, an oxygen gas is required essentially in the reaction and it is performed at a temperature of 40 to 60℃. Said oxygen gas reacts with phosphine, which is a ligand bonded with ruthenium, to convert to phosphine oxide. When the ruthenium complex of formula 7 is used, the reaction is performed at a temperature of 20 to 40℃. When the ruthenium complex of formula 10 is used, the reaction is performed at a temperature of 20 to 40℃. A base is also required to remove acid generated during the reaction. Said base includes triethylamine or diisopropylethyl amine but it is not limited to these examples.

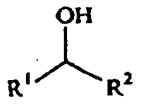
The ruthenium complex of formula 7 is commercially available and is converted to the ruthenium complex of formula 10 in alcohol/base condition. Therefore, results from the ruthenium complex of formula 7 and the ruthenium complex of formula 10 are almost same.

A mechanism of a reaction of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is described in detail hereunder.

An acyl group supplied from the acyl donor compound is reacted with lipase and this lipase is further reacted with one enantiomer of a racemic alcohol selectively to produce a chiral ester. The other enantiomer is racemized by reacting with ruthenium complex. And further one enantiomer from this racemic alcohol is acylated selectively by lipase and this reaction is repeated to produce optically pure chiral ester with preventing generation of ketone which is a by-product in conventional dynamic kinetic resolution.

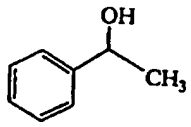
Reaction solvent is not limited but it is preferred to use methylene chloride, toluene, benzene, or hexane because a solvent commonly affects production yield in enzymatic catalysis reaction. An amount of said solvent is used to be 0.2 to 0.3 M concentration of a racemic alcohol.

Said racemic alcohol is generally expressed in the formula 4. It is not limited but examples of the present invention are the following compounds 4a, 4b, 4c, 4d, 4e or 4f,

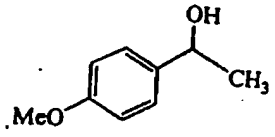


(4)

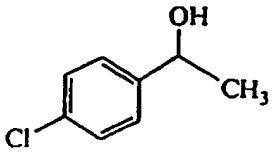
wherein R^1 and R^2 are the same as defined above.



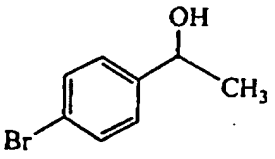
(4a)



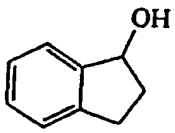
(4b)



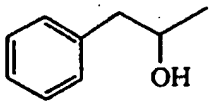
(4c)



(4d)



(4e)



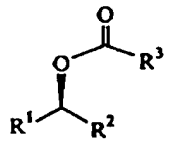
(4f)

Said lipase, which is esterase, acylates one enantiomer from a racemic alcohol selectively to a chiral ester. Examples of lipase are *Pseudomonas cepacias* lipase and *Candida antarctica* lipase and more particulary, *Candida antarctica* component B lipase supported on acrylic resin (Novozym 435, Novo company) or *Pseudomonas cepacias* lipase supported on ceramic particle (lipase PS-C, Amano company). An amount of said lipase is in the range of 10 to 60mg, preferably 30 mg, relative to 1 mmol of an alcohol in Novozym 435 case, and is in the range of 50 to 320 mg, preferably 160 mg, relative to 1 mmol of an alcohol in lipase PS-C case.

Said acyl donor supplies an acyl group to a lipase and acts to move a reaction balance to an acylated product in the presence of a lipase. Preferred acyl donor is aryl ester or alkenyl acetate, the most preferably aryl ester such as

p-chlorophenyl acetate having electron withdrawing group. An example of alkenyl acetate is isoprophenyl acetate. Such acyl donor compounds are preferred to use because they have an appropriate reactivity without inhibiting racemization. A preferred amount of said acyl donor compound is 2 to 4 equivalents to 1 equivalent of racemic alcohol. If the amount is more than 4 equivalents to 1 equivalent of racemic alcohol, it is difficult to isolate after a reaction. On the other hand, if it is less than 2 equivalents to 1 equivalent of racemic alcohol, the rate of acylation becomes too slow.

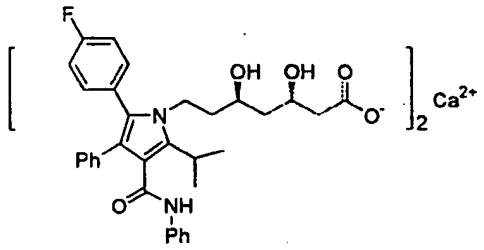
A chiral ester expressed in formula 100 is obtained by reacting a racemic alcohol, a ruthenium complex, a lipase, and an acyl donor compound,



(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

The chiral ester of formula 100 of the present invention can be used as a synthetic intermediate for preparing various chiral compounds, chiral pharmaceutical drugs or chiral agrochemicals and more particularly, used as an essential intermediate for preparing Atorvastatin expressed in formula 101 which is a useful drug for treatment for hyperlipemia, L-Carnitine expressed in formula 102 which is as an additive used in food and drugs, and Agenerase expressed in formula 103 which is an essential intermediate of AIDS drug.



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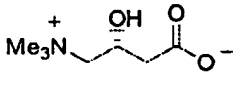

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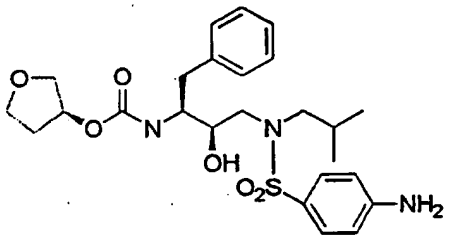
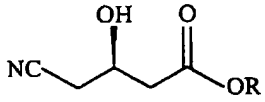


(103)

Especially, a chiral compound of formula 100a which is one of the compounds of the present invention is a key intermediate for preparing Atorvastatin of formula 101 disclosed in US Patent No. 5,908,953,



(100a)

wherein R is a low alkyl group.

The process for preparing a chiral ester of formula 100 of the present invention provides minimum production of by-products such as unreacted alcohol residue up to less than 10% and maximum production of product up to 98% having a high optical purity of 99% or more. Because optical purity is the most important factor in preparing chiral compounds for food and pharmaceutical drugs, the chiral ester of the present invention can be used as a useful starting material in various fields, especially fine chemical field.

The following examples are intended to be illustrative of the present invention and should not be construed as limiting the scope of this invention defined by the appended claims.

Example 1

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.75mmol), ruthenium complex of formula 6(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 2.0ml of dichloromethane to give a redish brown suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition. Oxygen(0.0130mmol) was injected with syringe in the reaction suspension and then it was heated at 60℃ for 43 hours.

Examples 2-6

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 7

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 7(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

Examples 8-12

The product, chiral ester, was prepared by the same procedure of Example 6 except to use racemic alcohols of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 13

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 10(0.0100mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

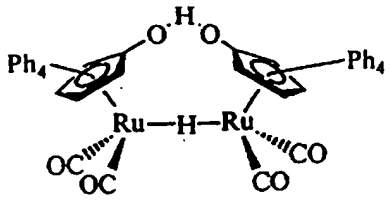
Examples 14-18

The product, chiral ester, was prepared by the same procedure of Example 11 except to use a racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Comparative Example 1

A racemic alcohol of formula 4a(2mmol), ruthenium complex expressed in the following structure below(0.04mmol), 60mg of Novozym 435, and *p*-chlorophenyl acetate(6mmol) were mixed in 5ml of toluene to give a dark redish suspension.

The reaction suspension was heated at 70℃ for 46 hours under argon gas.



Comparative Examples 2-5

The product, a chiral ester, was prepared by the same procedure of Comparative Example 1 except to use racemic alcohols of formulas 4b, 4d, and 4e and octan-2-ol instead of a racemic alcohol of formula 4a.

Yield, optical purity, and formation of ketone of each reaction of Examples 1-15 and Comparative Examples 1-5 were determined and tabled in Table 1. Said yield was analyzed by ^{1}H-NMR spectrum, and said optical purity was determined by high performance liquid chromatography. Said ^{1}H-NMR spectrum was taken by using Bruker AM 300 and said high performance liquid chromatography was SpectraSystem P2000.

Table 1

Section	Formation of ketone (%)	Yield (%)	Optical purity (e.e.%)
Example 1	0	85	96
Example 2	0	82	99
Example 3	0	98	99
Example 4	0	91	95
Example 5	0	85	97
Example 6	0	92	96
Example 7	8	90	94
Example 8	10	90	99
Example 9	8	90	99

Example 10	8	92	99
Example 11	8	83	99
Example 12	7	91	98
Example 13	5	95	94
Example 14	7	93	99
Example 15	5	93	97
Example 16	4	96	99
Example 17	4	85	99
Example 18	4	95	99
Comp. Example 1	20	Below 80	-
Comp. Example 2	40	Below 60	-
Comp. Example 3	22	Below 78	-
Comp. Example 4	23	Below 77	-
Comp. Example 5	20	Below 80	-

As shown in Table 1, the amount of a ketone formed as a by-product in Comparative Examples 1 to 5 is in the range of 20 to 40% while that in Examples 1 to 18 is less than 10%. Therefore, the yield of the final product, a chiral ester, prepared by Examples 1 to 18 is much more improved.

As a result, it is proved that the present invention provides a process for preparing an optically pure chiral ester from a racemic alcohol with minimizing the formation of ketone at a high yield in the presence of catalysts which are ruthenium complex selected from formulas 1, 2, and 3, and lipase.

CLAIMS

What is claimed is :

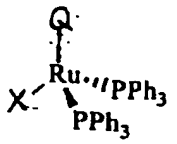
1. A process for preparing a chiral ester expressed in formula 100 by reacting;

a racemic alcohol of formula 4;

a ruthenium complex selected from the group consisting of compounds 1, 2, and 3 expressed in formulas 1, 2, and 3 to activate racemization of said racemic alcohol;

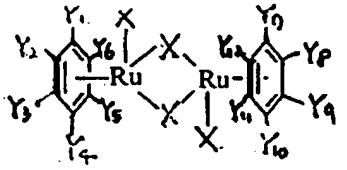
a lipase to acylate one enantiomer selectively from said racemic alcohol; and

an acyl donor compound to supply acyl group to said lipase,



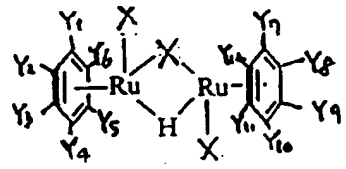
(1)

wherein Q is  or  ; and X is Br, Cl or I;



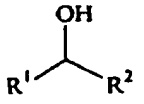
(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and



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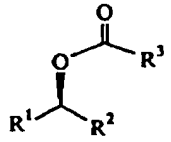
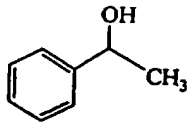


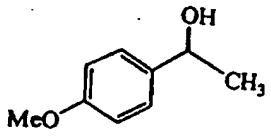
(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

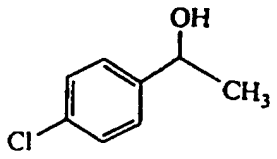
2. The process for preparing a chiral ester according to claim 1, wherein said racemic alcohol is selected from the group consisting of the compounds 4a, 4b, 4c, 4d, 4e and 4f.



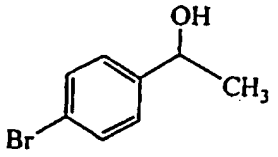
(4a)



(4b)



(4c)



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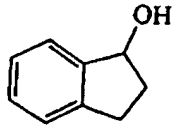

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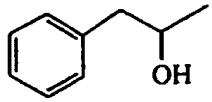
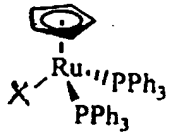


(4f)

3. The process for preparing a chiral ester according to claim 1, wherein said lipase is selected from the group consisting of *Pseudomonas cepacias* lipase and *Candida antarctica* lipase.

4. The process for preparing a chiral ester according to claim 1, wherein said ruthenium complex is selected from the group consisting of compounds 5, 6, 7, 8, 9, 10, 11 and 12,



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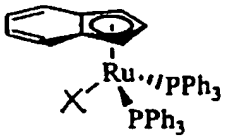

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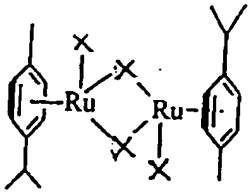

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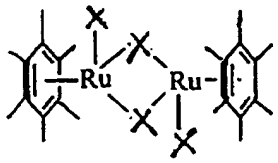

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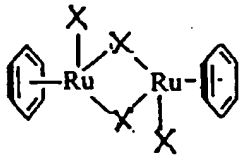

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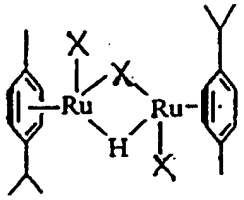

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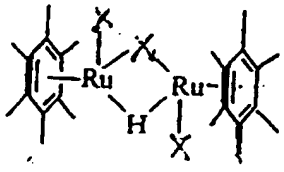

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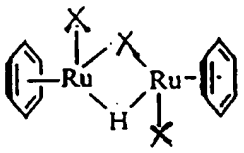

(12)

wherein X is Cl, Br or I, the most preferably Cl.

5. The process for preparing a chiral ester according to claim 3, wherein X is Cl.

6. The process for preparing a chiral ester according to claim 1, wherein said reaction requires use of oxygen gas.

7. The process for preparing a chiral ester according to claim 1, wherein a content of said ruthenium complex or its derivatives is in the range of 0.1 to 5mol% to said racemic alcohol.

8. The process for preparing a chiral ester according to claim 1, wherein said acyl donor compound is aryl ester.

9. The process for preparing a chiral ester according to claim 7, wherein said aryl ester is selected from the group consisting of *p*-chlorophenyl acetate and alkenyl acetate.

INTERNATIONAL SEARCH REPORT

international application No.
PCT/KR00/01170

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07C 67/00, C12P 7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
C07C, C12P

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
STN(REGISTRY, CAPLUS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T,A	Novel synthetic routes to several new, differentially substituted ruthenium tris(4,4'-disubstituted-2,2-bipyridine) complexes, Dusan Hsek et al, page 308-316, American Chemical Society (2000), 39(2) see the scheme 1 and table 1	1-9
T,A	Catalytic asymmetric and chemoselective aerobic oxidation : kinetic resolution of sec-alcohols, Masutani K. et al, page 5119-5123, Tetrahedron letters (2000) 41(26) see the page 5120(reaction, scheme) and table 1	1-9
T,A	synthesis of ruthenium complexes with planar-chiral cyclopentadienyl-pyridine or -phosphine bidentate ligands, Noriko Dodo et al, page 35-41, Dalton (2000) 1, Royal Society of chemistry see the scheme 2 and 5	1-9
A	EP-A2-375417 see the whole document	1-9
P,A	EP-A1-992481 see the whole document	1-9
A	Ruthenium(2)-catalyzed asymmetric transfer hydorgenation of ketones using a formic acid-triethylamine mixture, Fujii, Akio et al, page 2521-2, American Chemical Society (1996),	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 FEBRUARY 2001 (09.02.2001)	12 FEBRUARY 2001 (12.02.2001)

Name and mailing address of the ISA/KR	Authorized officer
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Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5536

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2-375417	1990.6.27	JP-A2-02-169555	1990.6.29
EP-A1-992481	2000.4.12	DE-A1-1998-5517 JP-A2-2000-119217	2000.4.6 2000.4.25

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